



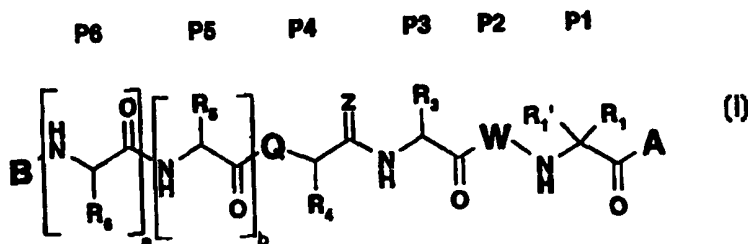
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## (57) Abstract

Compound of formula (I) active against the Hepatitis C virus, wherein when Q is CH<sub>2</sub>, a is 0, b is 0 and B is an amide derivative; or when Q is N-Y wherein Y is H or C<sub>1-6</sub> alkyl, then B is an acyl derivative; R<sub>6</sub>, when present, is C<sub>1-6</sub> alkyl substituted with carboxyl; R<sub>5</sub>, when present, is C<sub>1-6</sub> alkyl optionally substituted with carboxyl; when Q is either CH<sub>2</sub> or N-Y, then Z is oxo or thioxo; R<sub>4</sub> is C<sub>1-10</sub>alkyl, C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkylcycloalkyl); R<sub>3</sub> is C<sub>1-10</sub> alkyl optionally substituted with carboxyl, C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkylcycloalkyl); W is a proline derivative; R<sub>1</sub>' is hydrogen, and R<sub>1</sub> is C<sub>1-6</sub> alkyl optionally substituted with thiol; or R<sub>1</sub> is C<sub>2-6</sub> alkenyl; or R<sub>1</sub>' and R<sub>1</sub> together form a 3- to 6-membered ring; and A is hydroxy or a pharmaceutically acceptable salt or ester thereof.



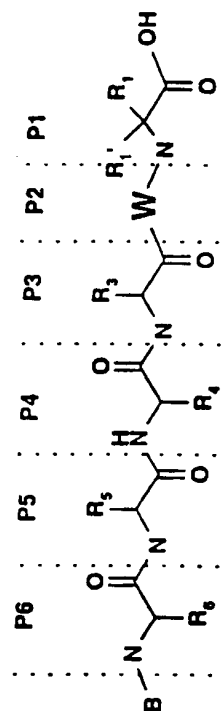
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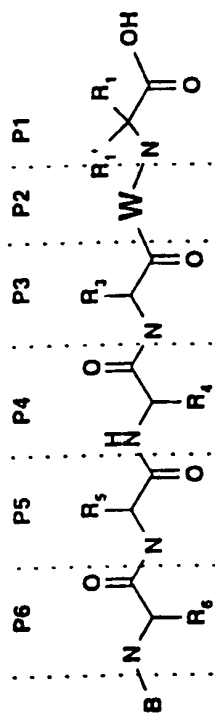
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- acetic acid); **Hyp**: 4(R)-hydroxyproline; **Hyp(4-Bn)**:  
4(R)-benzyloxyproline; **Pip**: pipecolic acid (i.e.  
homoprolyl); **Tbg**: tert-butylglycine; **Ac**: acetyl; **Bn**:  
benzyl; **O-Bn**: benzyloxy; **DAD**: 3-carboxypropionyl; and  
5 **DAE**: 4-carboxybutyryl; **AlGly**: allylglycine (2-amino-  
4-pentenoic acid); **thioxoIle**: L-thionoisoleucine; **Ph**:  
phenyl; **3I-Ph**: 3-iodophenyl; **4I-Ph**: 4-iodophenyl;  
**2Br-Ph**: 2-bromophenyl; **3Br-Ph**: 3-bromophenyl; **4Br-Ph**:  
4-bromophenyl; **1-NpCH<sub>2</sub>O**: naphthalen-1-ylmethoxy; 2-  
10 **NpCH<sub>2</sub>O**: naphthalen-2-ylmethoxy **3,5-Br<sub>2</sub>Ph**: 3,5-  
dibromophenyl.

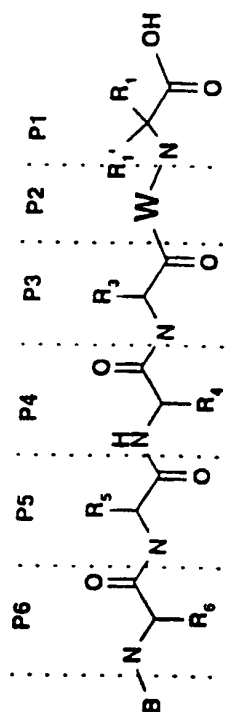
TABLE 1



Compound	B	P6	P5	P4	P3	W	P1	IC <sub>50</sub> ( $\mu$ M)	HLE ( $\mu$ M)	PPE ( $\mu$ M)	Other ( $\mu$ M)	MS (MH <sup>+</sup> )	AAA (%)
101	Ac	Asp	Asp	Ile	Val	Pro	Cys	46				703	113
102	Ac	Glu	Asp	Ile	Val	Pro	Cys	59				717	85.4 $\pm$ 1.6
103	DAD	---	Asp	Ile	Val	Pro	Cys	26				646	100.3 $\pm$ 1.8
104	Ac	Asp	D-Asp	Ile	Val	Pro	Cys	8.5				703	113.85 $\pm$ 4.9
105	Ac	Asp	D-Glu	Ile	Val	Pro	Cys	1.5				717	95.8 $\pm$ 0.8
106	Ac	Asp	Glu	Ile	Val	Pro	Cys	16*				717	98.8 $\pm$ 2.6
107	Ac	Asp	Val	Ile	Val	Pro	Cys	85*				687	85.9 $\pm$ 1.1
108	Ac	Asp	Tbg	Ile	Val	Pro	Cys	31				701	101.15 $\pm$ 1.65
109	Ac	Asp	Asp	Val	Val	Pro	Cys	80*				689	99.2 $\pm$ 5
110	Ac	Asp	Asp	Chg	Val	Pro	Cys	24*				729	102.95 $\pm$ 3.65
111	Ac	Asp	Asp	Tbg	Val	Pro	Cys	79				703	
112	Ac	Asp	Asp	Leu	Val	Pro	Cys	92*				703	109.7 $\pm$ 6.9
113	Ac	Asp	Asp	Ile	Ile	Pro	Cys	56*				717	72.4 $\pm$ 2.4
114	Ac	Asp	Asp	Ile	Chg	Pro	Cys	50*				743	103.65 $\pm$ 3.8
115	Ac	Asp	Asp	Ile	Val	Abu	Cys	58*				691	59.4 $\pm$ 2.85
116	Ac	Asp	Asp	Ile	Val	Leu	Cys	16*				719	95.4 $\pm$ 1.5

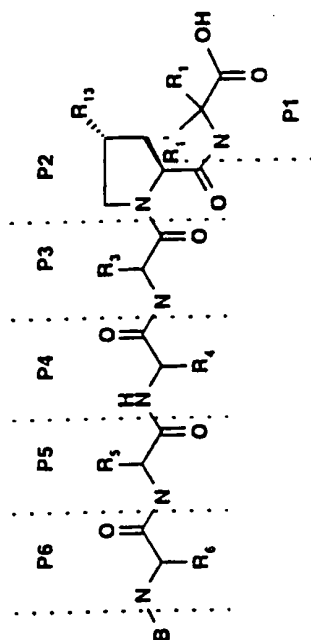


Compound	B	P6	P5	P4	P3	W	P1	IC <sub>50</sub> ( $\mu$ M)	HLE ( $\mu$ M)	PPE ( $\mu$ M)	Other ( $\mu$ M)	MS (MH <sup>+</sup> )	AAA (%)
117	Ac	Asp	Asp	Ile	Val	Phe	Cys	25*				753	99.6
118	Ac	Asp	Asp	Ile	Val	Val	Cys	133*				705	96.8 $\pm$ 1
119	Ac	Asp	Asp	Ile	Val	Ile	Cys	90				719	87.0 $\pm$ 3.0
120	Ac	Asp	Asp	Ile	Val	Ala	Cys	76*				677	N.S.
121	Ac	Asp	Asp	Ile	Val	Hyp(4-Bn)	Cys	1.7				809	101
122	Ac	Asp	Asp	Ile	Val	Pro	Abu	315				685	91.0 $\pm$ 4.5
123	Ac	Asp	Asp	Ile	Val	Pro	Nva	220	>300	>300		699	107.6
124	Ac	Asp	Asp	Ile	Val	Pro	AlGly	210				697	106.3 $\pm$ 8.2
125	Ac	Asp	Asp	Ile	Val	Pro	Acpe	210				711	94.02 $\pm$ 3.19
126	Ac	Asp	Asp	Ile	Val	Pro	Acca	45				683	100.2
127	Ac	Asp	Asp	Ile	Val	Pip	Nva	605*				713	107
128	Ac	Asp	D-Glu	Ile	Val	Pro	Nva	7.4				713	100.9 $\pm$ 3.6
129	Ac	Asp	Tbg	Ile	Val	Pro	Nva	270*				697	99.8 $\pm$ 0.6
130	DAD	---	Asp	Ile	Val	Pro	Nva	123				642	107
131	Ac	Asp	Glu	Chg	Glu	Glu	Cys	24					
132	Ac	Asp	D-Glu	Chg	Glu	Glu	Acca	36					

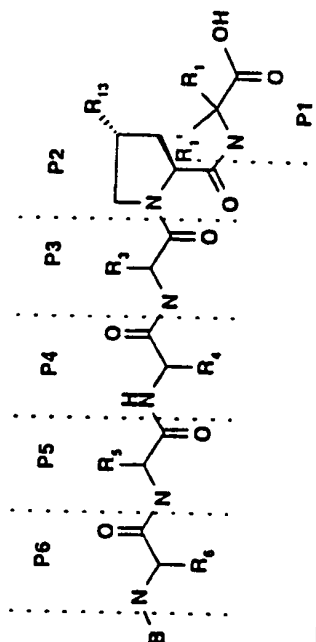


Compound	B	P6	P5	P4	P3	W	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
133	Ac	Asp	Glu	Chg	Val	Glu(OBn)	Acca	39					

TABLE 2

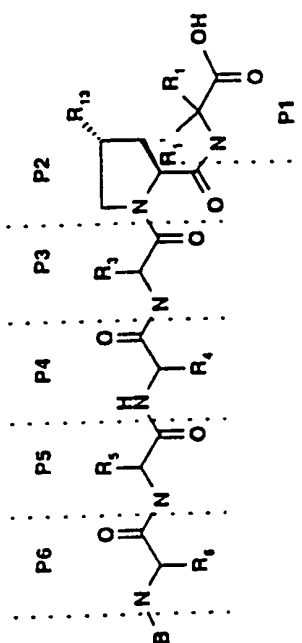


Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
201	Ac	Asp	Asp	Ile	Val	O-Bn	Nva	7.2				805	107
202	Ac	Asp	D-Val	Ile	Val	O-Bn	Nva	0.93				789	103
203	Ac	Asp	D-Glu	Ile	Val	O-Bn	Nva	0.6	>300	>300	>300**	819	96.3 ± 1.7
204	Ac	Asp	Asp	Ile	Val	<i>o</i> -tolyl-methoxy	Nva	9.4*				819	95
205	Ac	Asp	Asp	Ile	Val	<i>m</i> -tolyl-methoxy	Nva	6.7*				819	98.7
206	Ac	Asp	Asp	Ile	Val	<i>p</i> -tolyl-methoxy	Nva	6.4*				819	101.9
207	Ac	Asp	Asp	Ile	Val	1-NpCH <sub>2</sub> O	Nva	0.39				855	112
208	Ac	Asp	Asp	Ile	Val	2-NpCH <sub>2</sub> O	Nva	0.71				855	104
209	Ac	Asp	Asp	Ile	Val	4- <i>tert</i> -butyl-phenyl-methoxy	Nva	2.6				861	114
210	Ac	Asp	D-Glu	Chg	Val	O-Bn	Cys	0.033	>300	>300	>300	849	101.7 ± 5.4

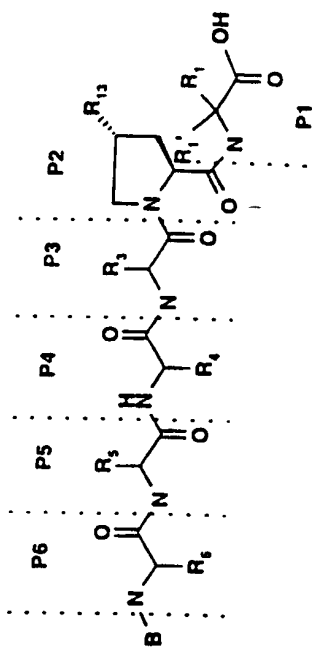


Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
211	Ac	Asp	D-Glu	Chg	Val	O-Bn	Nva	0.12				845	93.4 ± 2
212	Ac	Asp	D-Glu	Ile	Val	O-Bn	Acca	0.21	>300	>300		803	99.4 ± 2
213	Ac	Asp	D-Glu	Ile	Val	2-NpCH <sub>2</sub> O	Nva	0.036				869	101.8
214	Ac	Asp	D-Glu	Chg	Val	2-NpCH <sub>2</sub> O	Nva	0.028	>300	>300	>300 >300**	895	104.1
215	Ac	Asp	D-Glu	Chg	Val		Acca	0.014				879	---
216	Ac	Asp	Asp	Ile	Val	Bn	Nva	60				789	100.6 ± 0.8
217	Ac	Asp	Asp	Ile	Val	Ph(CH <sub>2</sub> ) <sub>3</sub> (	Nva	3				818	94.6 ± 3
218	Ac	Asp	D-Glu	Ile	Val	O-Bn	Nva	0.49				910	111.2
219	Ac	---	Asp	Ile	Val	1-NpCH <sub>2</sub> O	Nva	2.3				740	95.7
220	DAD	---	---	N(Me)Ile	Val	1-NpCH <sub>2</sub> O	Nva	31				697	---
221	DAD	---	---	Ile	Val	1-NpCH <sub>2</sub> O	Nva	22				683	---
222	DAE	---	---	Ile	Val	1-NpCH <sub>2</sub> O	Nva	20				698	N.S.
223		---	---	Ile	Val	1-NpCH <sub>2</sub> O	Nva	51				737	N.S.

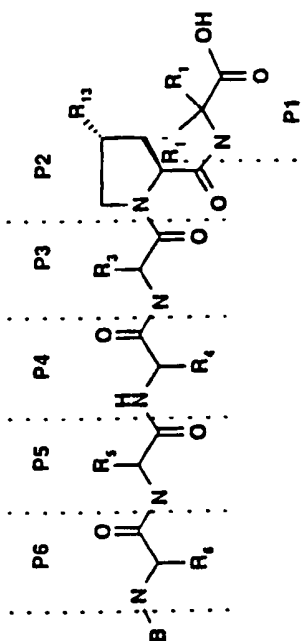


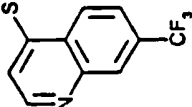
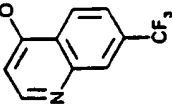


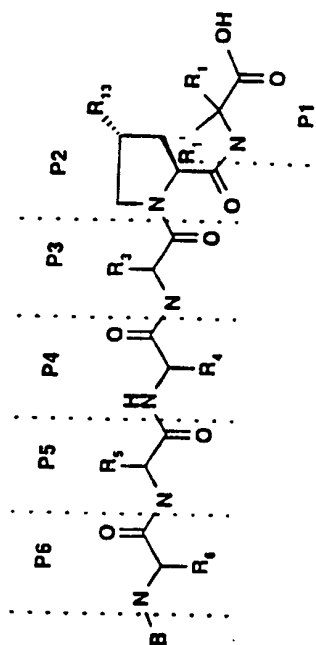
Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
224		---	---	Ile	Val	1-NpCH <sub>2</sub> O	Nva	56				737	N.S.
225	Ac	---	---	Ile	Val	1-NpCH <sub>2</sub> O	Nva	45				929	---
226	DAE	---	---	Chg	Val	1-NpCH <sub>2</sub> O	Acca	0.76				707	---
227	Ac	---	---	Chg	Val	1-NpCH <sub>2</sub> O	Acca	3	>600			635	
228	Ac	---	---	Chg	Val	O-Bn		35	>600			613.4	
230	Ac	Asp	Asp	Ile	Val	Ph(CH <sub>2</sub> ) <sub>3</sub>	Nva	3.3				818	
231	Ac	---	---	Chg	Chg	1-NpCH <sub>2</sub> O	Acca	2.6				675.4	
232	AcOCH <sub>2</sub> -C(O)	---	---	Chg	Chg	1-NpCH <sub>2</sub> O	Acca	1.4					
233	Ac	Asp	Glu	Ile	Val	(3I- Ph)CH <sub>2</sub> O	Acca	0.14				929.2	



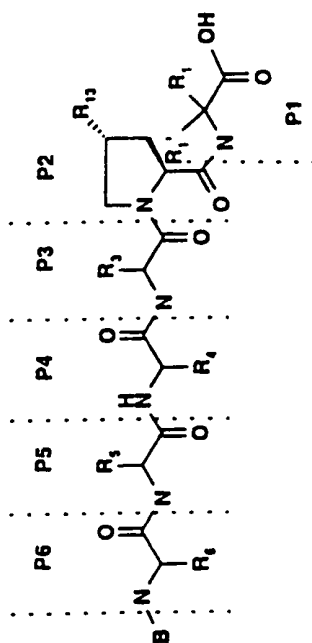
Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
234	Ac	---	---	Chg	Chg	O-Bn	Acca	41					
235	Boc	---	---	Chg	Chg	1-NpCH <sub>2</sub> O	Acca	12					
236	Ac	---	Gly	thioxo-Ile	Val	1-NpCH <sub>2</sub> O	Nva	4.0					
237	DAE	---	---	Ile	Val	1-NpCH <sub>2</sub> O	Acca	5.5				720 (M+Na)	
238	Ac	---	---	Chg	Val	(4Br-Ph)O	Acca	27				598 (M+Na)	
239	Ac	---	---	Chg	Val	(2Br-Ph)O	Acca	27	195				
240	Ac	---	---	Chg	Val	(3Br-Ph)O	Acca	42					
241	Ac	---	---	Chg	Val		Acca	18					
242	Ac	---	---	Chg	Val	(4Br-Ph)S	Acca	36					
243	Ac	---	---	Chg	Val		Acca	35					



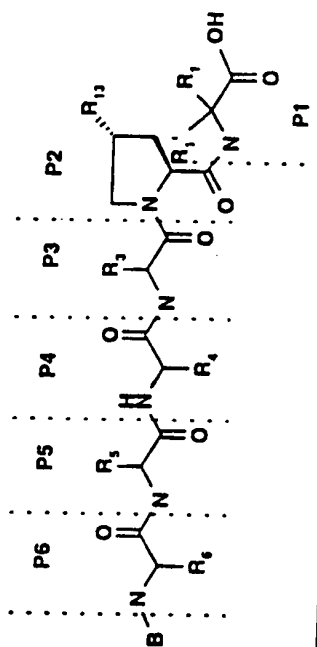
Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
244	Ac	---	---	Chg	Val		AcCa	10					
245	Ac	---	---	Chg	Val		AcCa	5.0					



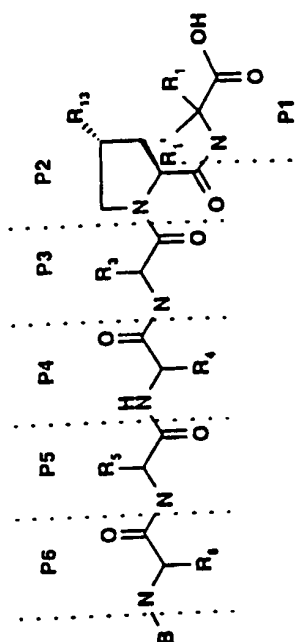
Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> ( $\mu$ M)	HLE ( $\mu$ M)	PPE ( $\mu$ M)	Other ( $\mu$ M)	MS (MH <sup>+</sup> )	AAA (%)
246	Ac	---	---	Chg	Val		Acca	33					
247	Ac	Asp	Asp	Ile	Val	Ph(CH <sub>2</sub> ) <sub>2</sub>	Nva	10					
248	Ac	---	---	Chg	Chg		Acca	3.6				803.6	119 $\pm$ 1
249	Ac	---	---	Chg	Val	(4I-Ph)O	Acca	9.7					

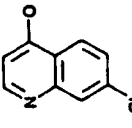
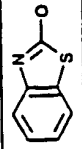
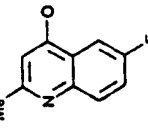


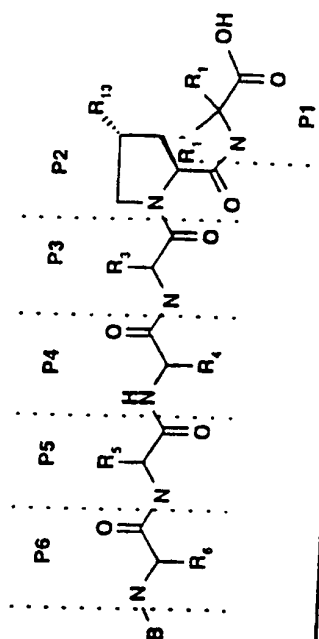
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250	Ac	---	---	Chg	Val		AcCa	4.5					
251	Ac	---	---	Chg	Val		AcCa	13					
252	Ac	---	---	Chg	Val	1-NpCH <sub>2</sub> O	Nva	20				651.4	91±1
253	Ac	---	---	Chg	Val		AcCa	28					



Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
254	Ac	---	---	Chg	Val		Acca	5.1					
255	Ac	---	---	Chg	Val		Acca	4.5					
256	Ac	---	---	Chg	Val		Acca	11					

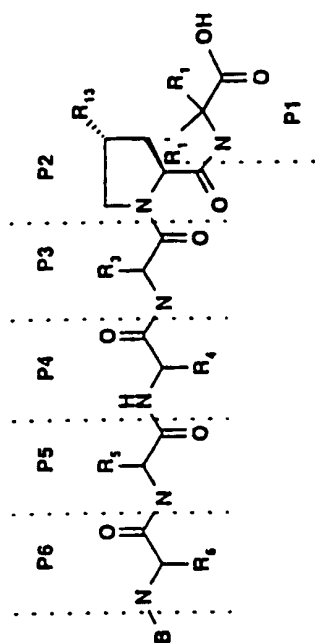


Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
257	Ac	---	---	Chg	Val		Acca	2.2	>300				
258	Ac	---	---	Chg	Val		Acca	16					
259	Ac	---	---	Chg	Val		Acca	28					
260	Ac	Asp	D-Glu	Ile	Val	O-Bn	Cys	0.18					
261	Ac	---	---	Chg	Val	O-Bn	Cys	28					
262	Ac	---	---	Ile	Val	1-NpCH <sub>2</sub> O	Acca	40				631 (M+Na)	

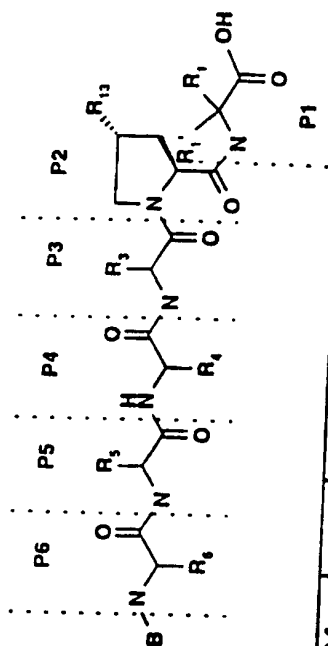


Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
263		---	---	Ile	Val	1-NpCH <sub>2</sub> O	AcCa	17				771 (M+Na)	
264		---	---	Ile	Val	1-NpCH <sub>2</sub> O	AcCa	6.4				811	
265		---	---	Ile	Val	1-NpCH <sub>2</sub> O	AcCa	10				811	
266		---	---	Ile	Val	1-NpCH <sub>2</sub> O	AcCa	9.7				721.4	





Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
267		---	---	Ile	Val	1-NpCH <sub>2</sub> O	Acca	12				721.4	
268	Ac	---	---	Chg	Val	(3Br-Ph)CH <sub>2</sub> O	Acca	24				665.1	
269		---	---	Chg	Val	1-NpCH <sub>2</sub> O	Acca	2.2				835.5 (M-H)	
270		---	---	Chg	Val	1-NpCH <sub>2</sub> O	Acca	2.0				745 (M-H)	



Comp.	B	P6	P5	P4	P3	R <sub>13</sub>	P1	IC <sub>50</sub> (μM)	HLE (μM)	PPE (μM)	Other (μM)	MS (MH <sup>+</sup> )	AAA (%)
271		---	---	Chg	Val	1-NpCH <sub>2</sub> O	Acca	3.8					
272	Ac	---	---	Chg	Val	(3,5-Br <sub>2</sub> -Ph)CH <sub>2</sub> O	Acca	27					
273	Ac	Asp	Asp	Ile	Val	H	Nva	17.5					
274	Ac	Asp	D-Val	Ile	Val	H	Cys	7.6					
275	Ac	---	---	Chg	Val		Acca	6.2					